



Management of Excessive Anticoagulant Effect Due to Vitamin K Antagonists

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Unexpectedly elevated INR values are commonly encountered in clinical practice. In the absence of bleeding, such values may be treated with either simple warfarin withdrawal or the administration of low doses of oral vitamin K. Oral vitamin K will more rapidly return the INR to the therapeutic reference interval; however, its impact on bleeding is unknown. If the INR is in excess of 10, most experts would recommend the administration of vitamin K and, in the case of active bleeding, additional administration of coagulation factors either in the form of fresh frozen plasma

(FFP) or prothrombin complex concentrates (PCC). Coagulation factor replacement is required given the need to urgently correct the INR; however, vitamin K should not be forgotten since it is required to antagonize the effect of warfarin, preventing “rebound” anticoagulation after transfused coagulation factors are consumed. This paper will review the evidence supporting various treatment modalities and will provide suggestions for treatment. Future advances in this area will likely focus on evaluations of the relative merits of FFP and PCCs.

Introduction

Due to its efficacy in reducing arterial and venous thromboembolic events oral vitamin K antagonist therapy (VKA) is used in more than 1% of adult population in Western countries.¹

Oral anticoagulants inhibit biosynthesis of vitamin K-dependent procoagulant factors II, VII, IX, and X,² reducing the coagulant potential of the blood. Monitoring of VKA is both required and challenging since VKA have a narrow therapeutic window and their anticoagulant effect is unpredictable. Even patients followed in specialized centers spend only about 60% of their time within the desired therapeutic range, and an excessive anticoagulant effect is frequently encountered in clinical practice.³ The anticoagulant effect of VKA is monitored with the international normalized ratio (INR); an excessively elevated INR independently predicts major bleeding. The risk of bleeding approximately doubles for each single point of increase in the INR above 3.0.^{4,5} Major hemorrhage occurs with a rate of 2.4% to 8% per patient-year.⁶ VKA increases the risk of intracranial hemorrhage (ICH) 7- to 10-fold, to a rate of nearly 1% per patient-year. ICH has an estimated 60% mortality rate.^{7,8} Although guidelines on the treatment of patients with supra-therapeutic INR with or without major hemorrhage have been published,^{9,10} these recommendations are largely based on opinion due to a lack of randomized trials.

Management of the Non-bleeding Patient with High INR

Potential treatment strategies in the management of non-bleeding patients with high INR include withholding VKA alone,

or withholding VKA and administering vitamin K. Transfusion therapy (either in the form of fresh frozen plasma or coagulation factor concentrates) is expensive, is potentially dangerous and should not be routinely used in these patients.

Conservative treatment of non-bleeding over-anticoagulated patients entails simply withholding VKA and allowing the INR to fall into the therapeutic range. This is the most widely used approach to the treatment of patients with warfarin-associated coagulopathy.^{11,12}

The recommendation to simply withhold VKA and allow the INR to fall into the desired range is supported by two case series in which a total of 352 INR values above 6.0 occurred in 299 patients. Only 2 patients (0.6%) suffered hemorrhage when treated with simple temporary withdrawal of VKA.^{11,12} In a more recent and larger series Garcia et al evaluated the 30-day incidence of major bleeding in patients with INR above 5¹²—this risk was low (1.3%). Vitamin K use in this study was infrequent. When patients with INR value above 9 were evaluated separately the 30-day risk of major bleeding was high (9.6%), calling into question the safety of this approach in patients with higher INR values.

Three studies have compared intravenous vitamin K in differing doses for the treatment of VKA-associated coagulopathy.¹³⁻¹⁵ These studies concluded that a 0.5 mg intravenous dose was optimal if the goal of therapy was to return the INR to the usual therapeutic range. Although anaphylactoid reactions have been described with the intravenous vitamin K1 most such cases occurred with large doses of vitamin K, administered rapidly and with little dilution. The best estimate of the frequency of this complication is about 3 per 10,000 doses administered; it may be

more likely if formulations containing polyethoxylated castor oil are used to maintain the vitamin K in solution.¹⁶ Modern formulations of vitamin K for intravenous injection utilize solubilizers that appear to be associated with a lower risk of anaphylaxis.

Subcutaneous vitamin K is widely used to treat warfarin-associated coagulopathy.^{17,18} However, it has unpredictable effects on the INR;^{19,20} we and others have recommended that intravenous vitamin K is preferred to subcutaneous vitamin K if rapid decreases in the INR are desired.

Vitamin K1 (phytonadione, a plant-derived form of vitamin K), when used orally in doses of 1 to 2.5 mg, does not produce warfarin resistance, or anaphylactoid or skin reactions.²¹⁻²⁷ Furthermore, oral vitamin K simplifies the out-of-hospital management of asymptomatic VKA-associated coagulopathy.

Several randomized controlled trials and a recent meta-analysis have found that low doses of oral vitamin K are effective for the reduction of excessively elevated INR values.^{23-25,28,31} However, a recent large randomized controlled trial including more than 700 patients with INR values between 4.5 and 10.0 failed to show a statistically significant reduction in major bleeding events in the group of patients randomized to 1.25 mg of oral vitamin K compared with the group of patients randomized to placebo.³² No studies have directly compared the efficacy of differing doses of oral vitamin K. A recent cumulative analysis of the available literature does suggest, however, that the optimal dose of oral vitamin K is 1 to 1.25 mg for patients with INR values between 4.5 and 10.0, and 2.5 mg for patients with INR values of more than 10.0.³³ When oral vitamin K is not available, the intravenous form of vitamin K can be mixed with orange juice, to mask its unpleasant flavor, and administered by mouth.^{22,23,25} In many jurisdictions the smallest available dose of vitamin K is a 5 mg tablet; this tablet is usually scored, allowing a 2.5 mg dose to be used.

Management of high INR values in the non-bleeding patients with mechanical heart valves (MHV) may be problematic because the risk of systemic embolism may be particularly high if the INR was over-corrected (particularly in those with mitral valves or older valves in the aortic position).

Our group has recently published a RCT in which we compared the effect of withholding warfarin and administering 1 mg oral vitamin K with simply withholding warfarin in asymptomatic patients with MHV presenting with INR values between 6.0 and 12.0.³⁴ Compared with placebo, 1 mg of oral vitamin K more commonly returned prolonged INR values to near therapeutic range within 1 day ($P < .001$). Furthermore, there was no significant difference between the two groups in the proportion of patients with INR values < 1.8 , and none of the patients in the study experienced a thrombotic or bleeding event during follow-up. However, because of the small sample and the short-

term follow-up of the study, inferences on thromboembolic and bleeding complications associated with the administration of small doses of vitamin K are of limited value.

Management of Patients Who Require Urgent Reversal of Anticoagulation

Patients who bleed while receiving VKAs or who need immediate surgery require urgent reversal of anticoagulation. Management of these patients must be individualized and depends on the severity and location of the hemorrhage and the INR when bleeding occurs. VKA therapy should be withheld in all patients with major bleeding during VKA therapy. Patients should receive intravenous vitamin K and coagulation factor replacement. Intravenously administered vitamin K works more rapidly than either oral or subcutaneous vitamin K.^{20,21,30} Reduction of the INR begins within 2 hours,³⁰ and a correction to within the normal range is generally achieved within 24 hours if hepatic function is normal and if a sufficiently large dose is given; low-dose vitamin K (0.5 to 1 mg) without coagulation factor replacement is inappropriate if the goal of therapy is rapid normalization of the INR.³⁵ FFP is widely available and provides rapid but partial reversal of the coagulopathy through the replacement of coagulation factors II, VII, IX, and X.³⁶ In the United States, FFP remains the most widely used coagulation factor replacement product for urgent reversal of VKA.¹⁸ The usual dose of plasma is 15 mL/kg, although the optimal dose has not been established.^{37,38} A lower dose (5 to 8 mL/kg) may be appropriate when urgent reversal of a therapeutic (rather than suprathreshold) INR is required.³⁹

Volume overload may make it difficult to administer an adequate FFP dose, particularly since patients often have compromised cardiovascular systems,⁴⁰ and in some patients who have profound decreases in vitamin K-dependent factors replacement of hemostatic levels of these factors cannot be achieved with tolerable doses of FFP. Furthermore, in many patients “usual” doses of FFP are insufficient to normalize IX levels.⁴¹ Since FFP contains isoagglutinins, it must be blood group specific.⁴² Furthermore, it must be thawed before use, which can delay treatment. Finally, there is a (low) risk of transfusion-transmitted infection.⁴³

Prothrombin complex concentrates (PCCs) provide a rapid and effective method for replacing deficient clotting factors and correcting the INR. It may be preferable to plasma if it is readily available. PCCs are intermediate-purity pooled plasma products containing factors II, IX, and X with variable amounts of FVII and natural anticoagulant proteins C and S.⁴⁴ They were previously used in the treatment of hemophilia B prior to the availability of high-purity plasma-derived and recombinant FIX concentrates.⁴⁵ In the first controlled trial, Taberner et al randomized 18 overanticoagulated patients to receive PCC or intravenous vitamin K.⁴⁶ Patients randomized to PCC had a more rapid INR correction compared to patients random-

ized to vitamin K. Several additional (but small) prospective studies have shown that PCC is effective in reducing INR and achieving rapid hemostasis in patients with major bleeding or who required urgent surgery.^{36,47,48} PCCs are likely to produce more rapid and complete INR reversal compared with FFP. In a study conducted on 41 patients who were bleeding because of warfarin overdosage or who required urgent reversal of warfarin therapy, Makris et al⁴⁹ compared the efficacy of PCC (25-50 U/kg) and FFP for rapidly reducing INR. Complete correction of the INR occurred within 15 minutes in 28 of 29 patients treated with PCC versus none of 12 patients treated with FFP. Similar results have been found by other investigators.^{40,50} However, whether PCC improves clinical outcome when compared with FFP is unknown. As with other coagulation factor concentrates there remains a risk of transfusion-transmitted infection; however, this risk is significantly reduced by procedures such as solvent/detergent-treatment and nanofiltration.⁴⁷

The optimal dose of PCC is not established, and some experts suggest that should be individualized according to initial INR, target INR and body weight. Furthermore, available data do not allow a direct comparison among different PCCs. In a randomized trial, Van Aart et al showed that the number of patients reaching the target-INR 15 minutes after the dosage of PCC was significantly higher in the group treated with an "individualized" dosage, compared to the group treated with a standard dose (89% vs 43%; $P < .001$).⁵¹ In another recent study, Yasaka et al⁵² found that 500 IU of the PCCs were sufficient for rapid correction of INR values below 5.0 but that they were inadequate in patients with INR values of 5.0 or more in patients with major hemorrhagic complications of anticoagulant treatment or who required invasive procedures.

Fear of thrombotic complications has limited the use of PCCs even in patients presenting with life-threatening hemorrhage. However, in a recent systematic review including 14 studies for a total of 460 patients, there were only 7 thrombotic complications (3 strokes, 2 myocardial infarctions and 2 deep vein thromboses).⁵³

When immediate correction of the INR is required clinicians oftentimes fail to administer vitamin K at the time that a coagulation factors are replaced. Failure to administer vitamin K may cause the INR to rise, usually 12 to 24 hours after initial treatment because the half-life of warfarin far exceeds the half-life of the administered coagulation factor complexes.⁵⁴

Recombinant FVIIa (rFVIIa) has been used in patients with acute intracerebral hemorrhage who were not receiving anticoagulant therapy.^{55,56} Although earlier results were promising,⁵⁵ a larger randomized trial failed to confirm rFVIIa reduced mortality.⁵⁶ rFVIIa has also been used for correction of warfarin associated coagulopathy; it effectively corrected the INR in healthy human volunteers receiving

acenocoumarol,⁵⁷ and it appears to rapidly correct the INR in excessively anticoagulated patients and in patients presenting with central nervous system bleeding emergencies.^{58,59} However, rVIIa causes thrombosis and there are few data to support its clinical efficacy; as a result its routine use should be avoided until better quality evidence supporting its effectiveness becomes available.⁶⁰ If rVIIa is used it is important to remember to administer vitamin K and to monitor closely for recurrent coagulopathy as it has a half-life of less than 60 minutes.⁶¹

Conclusion

Patients receiving VKA therapy frequently present with elevated INR values. In non-bleeding patients, low-dose oral vitamin K reduces the INR and may allow earlier reinstatement of warfarin. However, a recent randomized trial failed to show a reduction in the risk of bleeding.

Patients experiencing major or life-threatening bleeding should be treated with some form of coagulation factor replacement. Although preliminary evidence suggests that PCC may be superior to FFP in such patients, availability and physician familiarity with PCC is limited, suggesting that in most circumstances FFP will remain the preferred agent in North America. Specific, evidence-based recommendations for the treatment of bleeding in patients receiving VKA therapy cannot be made due to limited data; however, all patients should receive intravenous vitamin K and some form of coagulation factor replacement.

Disclosures

Conflict-of-interest disclosure: M.A.C. is a consultant for Artisan Pharma, Aton Pharma, and Bayer; receives research funding from Bayer, Boehringer-Ingelheim, Astra-Zeneca, the Heart and Stroke Foundation of Canada and the Canadian Institutes of Health Research; receives direct unrestricted research support from Sanofi-Aventis and Leo Laboratories; and receives honoraria from Pfizer, Leo Laboratories, Organon, and Novo Nordisk. F.D. declares no competing financial interests.

Off-label drug use: None disclosed.

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